A New Approach to Combatting Iodine Deficiency in Developing Countries: The Controlled Release of Iodine in Water by a Silicone Elastomer

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ABSTRACT

Objectives. Four hundred million people or more may be exposed to iodine deficiency worldwide, in developing countries in particular. Because of the practical problems with existing methods for the large-scale prevention of iodine deficiency, the authors developed a new approach to collective prophylaxis.

Methods. This approach relies on the controlled diffusion of iodine into water from a silicone elastomer. Silicone matrices installed in a bore well released iodine at a rate sufficient to permit the daily per capita intake of at least 100 μg of iodine, the amount recommended by the World Health Organization. The matrices were tested over 1 year in a village in Mali, West Africa, an area in which goiter was highly endemic. The effects on the well water and population were compared with those of a placebo system in a control village.

Results. An increase in urinary iodine levels was observed in the treated population, and after 12 months the incidence of goiter had fallen from 53.2% to 29.2%.

Conclusions. This new concept, adaptable to all sources of water supply, may contribute to the eradication of iodine deficiency. (*Am J Public Health.* 1993;83:540–545)

Introduction

As many as 400 to 800 million people may be exposed to iodine deficiency throughout the world.[1] This deficiency is responsible for various disorders grouped under the heading of iodine deficiency disorders: goiter, hypothyroidism, impaired mental function, spontaneous abortions, stillbirths, congenital anomalies, increased perinatal and infant mortality, and neurological and myxedematous cretinisms.[2] The main methods used to combat iodine deficiency in developing countries have been the following:

- Iodization of salt, a costly method that requires special packaging and the existence of national commercial networks, which are currently insufficient.[3]
- Intramuscular injections of iodinated oil, an individual method of protection that is demanding because it requires medical intervention; the disposable injection equipment that is required increases the cost per annum and per subject considerably.[1,3]
- Oral intake of iodinated oil, an individual method of prevention whose duration of protection is inadequate, given the cost; it requires the setting up of a distribution infrastructure, and long-term compliance with treatment has been poorly assessed.[3–5]

Because of these problems with existing methods of iodine deficiency prevention, we developed a method of collective prevention using a vehicle that is both ubiquitous and a dietary staple: water. The iodine supplementation of water from any source is accomplished by means of a silicone elastomer device that releases a physiological amount of iodine (>100 μg per day) over a 1-year period. No specialized skills are required to set up the method and no special contribution is required from the populations. The device was initially developed in the laboratory and the laboratory results were then tested in the field (Mali, West Africa).

Methods

Development of the Controlled Release System

The aim was to prepare a controlled release system based on silicone and an iodine salt that would release amounts of iodine over a 1-year period so that individuals obtaining their water from the source would receive a daily intake of iodine in excess of 100 μg, the amount recommended by the World Health Organization. Silicones were selected because they are chemically and biologically inert, nontoxic, nonirritant, stable over time and over a wide range of temperatures, sterilizable, and highly permeable to small molecules and gases.[6] Sodium iodide (NaI)

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was chosen as the iodine compound for its optimum iodide/active ingredient weight ratio. The controlled release system consists of a matrix formed of a silicone elastomer cross-linked with platinum (RTV 70141) containing a dispersion of NaI in powdered form; it is consistent with United States Pharmacopeia requirements.[7]

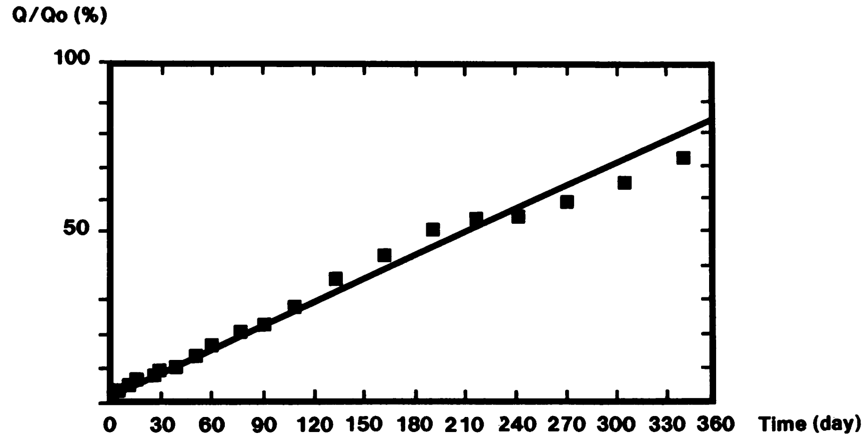
In general, diffusion of a molecule that is dissolved or dispersed in a polymer is governed by Fick's law and the kinetics of its release are of a fractional order with respect to time.[8,9] Studies of the silicone NaI system demonstrated that release of NaI was a zero order process with respect to time (more than 80% of the active ingredient was released according to these kinetics). On the other hand, elution was a function of the particle size distribution and the percentage of NaI in the matrix, the degree of cross-linking of the elastomer, and the area/volume ratio of the object.

In vitro release kinetics were measured by placing a matrix in 1 L of distilled water, which was then stirred. The amount of material released was measured by assaying the I ion by titration against silver nitrate.

Silicone is highly permeable to water vapor, which penetrates the material and dissolves the salt. When surface osmotic pressure becomes greater than the material's tear resistance, the network ruptures and micropores are created, releasing the salt solution. A matrix was developed that released 80% of the NaI over a 1-year period by adjusting the parameters governing elution. The matrix consists of a cylinder with a diameter of 3.1 cm and a height of 10.0 cm filled with 30% of NaI (weight = 100 g). Starting with this basic model, we devised a system capable of continuously releasing 720 mg of iodide ion per day (720 mg = $a/b \times c \times 24$), given that release requirements depended on the iodide intake desired per person per day (a = 0.1 mg), the average daily consumption of water (b = 2 L) and the flow rate of the bore well (c = 600 L/h).

Fifteen cylinders were placed in an open-work food-grade polyethylene basket with five levels, each containing three cylinders. The diameter of the basket is such that it can be introduced into any bore well currently being exploited anywhere in the world. The system is very flexible because the desired concentration (50 μg/L or more) can be attained simply by adjusting the number of matrices to the hourly flow rate of the water source. The iodine released by a basic matrix is constant irrespective of flow rate.

Iodine concentrations in water of around 50 μg/L were obtained over a 1-year period when the system was tested in vitro at a flow rate of 600 L/hr (Figure 1). The rate of release was independent of temperature (from 10° to 50°C) of the con-



Note. Q/Qo = quantity of iodine salt released as a percentage of initial total quantity.

FIGURE 1—Cumulative annual release of iodine (experimental data).

TABLE 1—Iodine Water Concentrations (μg/L) in Test and Control Villages at Noon and at 6 PM at Varying Intervals, from 15 Days before the Start of the Experiment (on Day 0) to 12 Months after the Start

		Test Village	Control Village
Day 0 – 15 days	Noon	6	3
	6 PM	4	4
Day 0 – 8 days	Noon	3	<3
	6 PM	3	3
Day 0	Noon	4	4
	6 PM	3	4
Day 0 + 10 days	Noon	107	5
	6 PM	189	2
Day 0 + 15 days	Noon	158	4
	6 PM	198	4
Day 0 + 21 days	Noon	313	3
	6 PM	133	6
Day 0 + 1 month	Noon	81	4
	6 PM	122	2
Day 0 + 2 months	Noon	234	3
	6 PM	136	3
Day 0 + 3 months	Noon	116	4
	6 PM	153	2
Day 0 + 4 months	Noon	159	4
	6 PM	119	2
Day 0 + 5 months	Noon	119	<2
	6 PM	216	3
Day 0 + 6 months	Noon	159	7
	6 PM	190	2
Day 0 + 7 months	Noon	219	<2
	6 PM	263	<2
Day 0 + 8 months	Noon	179	<2
	6 PM	170	<2
Day 0 + 9 months	Noon	156	3
	6 PM	208	2
Day 0 + 10 months	Noon	113	<2
	6 PM	139	2
Day 0 + 11 months	Noon	151	3
	6 PM	140	3
Day 0 + 12 months	Noon	34	4
	6 PM	100	3

TABLE 2—Urinary Iodine Levels and Urinary Iodine:Creatinine Ratios in Test and Control Villages at 90-Day Intervals over a Period of 1 Year

	Test Village Iodine (SD)	Control Village Iodine (SD)	Test Village Iodine: Creatinine (SD)	Control Village Iodine: Creatinine (SD)	*t* Test
Day 0	13 (26)	14 (17)	15 (29)	35 (49)	Iodine = $\lvert 0.32 \rvert$ $P > .05$ Iod/creat = $\lvert 3.54 \rvert$ $P < .01$
Day 90	108 (132)	13 (19)	126 (149)	19 (31)	Iodine = $\lvert -7.28 \rvert$ $P < .01$ Iod/creat = $\lvert -7.09 \rvert$ $P < .01$
Day 180	317 (181)	15 (21)	966 (2518)	60 (198)	Iodine = $\lvert -16.73 \rvert$ $P < .01$ Iod/creat = $\lvert -3.59 \rvert$ $P < .01$
Day 270	182 (87)	11 (32)	482 (706)	27 (65)	Iodine = $\lvert -19.35 \rvert$ $P < .01$ Iod/creat = $\lvert -6.10 \rvert$ $P < .01$
Day 360	173 (86)	9 (18)	448 (741)	15 (33)	Iodine = $\lvert -18.84 \rvert$ $P <.01$ Iod/creat = $\lvert -5.80 \rvert$ $P < .01$
t test	D0-D90 = $\lvert -7.18 \rvert$ $P < .01$ D0-D180 = $\lvert -16.77 \rvert$ $P < .01$ D0-D270 = $\lvert -17.63 \rvert$ $P < .01$ D0-D360 = $\lvert -17.86 \rvert$ $P < .01$	D0-D90 = $\lvert -0.54 \rvert$ $P < .05$ D0-D180 = $\lvert -0.45 \rvert$ $P < .05$ D0-D270 = $\lvert -0.82 \rvert$ $P < .05$ D0-D360 = $\lvert -2.15 \rvert$ $P < .05$	D0-D90 = $\lvert 7.43 \rvert$ $P > .01$ D0-D180 = $\lvert -3.78 \rvert$ $P > .01$ D0-D270 = $\lvert 6.28 \rvert$ $P > .01$ D0-D360 = $\lvert 5.81 \rvert$ $P < .01$	D0-D90 = $\lvert 2.66 \rvert$ $P < .01$ D0-D180 = $\lvert -1.21 \rvert$ $P > .05$ D0-D270 = $\lvert 0.92 \rvert$ $P > .05$ D0-D360 = $\lvert 3.27 \rvert$ $P < .01$	

Note: D = day; iod/creat=iodine/creatinine.

centration of iodide ion in the elution phase (up to concentrations equal to 10% of sodium iodide in water) and was independent of water hardness and pH.

Field Study

Mali is a Sudanese-Sahel country in West Africa where goiter is highly endemic.[1] At the start of the investigation, its population consisted of 8 505 000 inhabitants.[10] The study was carried out from November 1988 to November 1989 in two remote villages in the Neguela District (Koulikoro Region), Woloni and Sirablo, situated 37 km and 25 km, respectively, from the nearest tarred road. The two villages were approximately 60 km from Bamako and were separated from one another by 28 km of dirt track. Each village had a single source of water, consisting of a bore well with a manual pump (India, Mark II) in Palaeozoic and upper pre-Cambrian crystalline rock. Woloni's well was 96 m deep and Sirablo's well was 75 m deep. The two village populations tend not to travel far and journeys exceeding 20 km are considered exceptional.

The study used a double-blind design. Measures employed in analysis were (1) concentration of iodine in the water as a function of time, (2) urinary iodine levels, and (3) size of goiters in the populations of the two villages. The authorization of the Republic of Mali Ministry of Public Health and the informed consent of the village populations concerned (as expressed by the traditional chief) were obtained before a device containing iodine was immersed in Woloni's well and a similar device not containing iodine was immersed in Sirablo's well on day 0. The entire zone of investigation was excluded from any other measure for combating iodine deficiency. One investigating physician and one sociologist stayed permanently in the two villages throughout the duration of the study, paying particular attention to monitoring external food and drug supplies.

Timetable and methods used for measuring the parameters. The borehole water was sampled at noon, and 6 PM on three occasions before installation of the device (day -15, day -8, and day 0); on days 2, 10, 15, 21, and 30; and then every month up until the 12th month. Water samples were collected in polypropylene vials containing 0.5 g of sodium carbonate.

Urine samples were taken from a representative sample of each of the two village populations on day 0, then after 3 months, 6 months, 10 months, and 12 months. The urine samples were collected in polypropylene vials containing 0.1 g of thymol and were assayed for iodine and creatinine. Successive samplings were taken at random, drawing from the population census register made at the start of the investigation.

We used the World Health Organization grade classification[11] to evaluate the prevalence of goiter on day 0, after 6 months, and after 12 months for the entire population of the two villages present at the time of the examinations.

Assay methods. The iodine content of water and urine were determined, after prior mineralization of the test sample in alkaline medium, by a method based on the redox properties of iodine. Final measurement was made with ultraviolet spectrophotometry. The creatinine content of urine was measured by the Bartels method, using the Jaffé reaction without deproteinization.

Statistical methodology. Data were analyzed with the SAS system (SAS Institute, Cary, NC). The statistical analyses consisted of (1) a test to validate the normality of the population samples studied; (2) a comparison of percentages by means of the χ^2 test, so as to compare the structure of the populations studied and changes in the prevalence of goiter; (3) unpaired *t* tests to compare mean urinary iodine levels as a function of time; and (4) the general linear model procedure to compare the urinary iodine levels and urinary iodine:creatinine ratios of the two villages, and also to compare the iodine content of the two villages' well water and iodine content as a function of time. Direct standardization was used to adjust age and sex in the control village on those in the test village.

Results

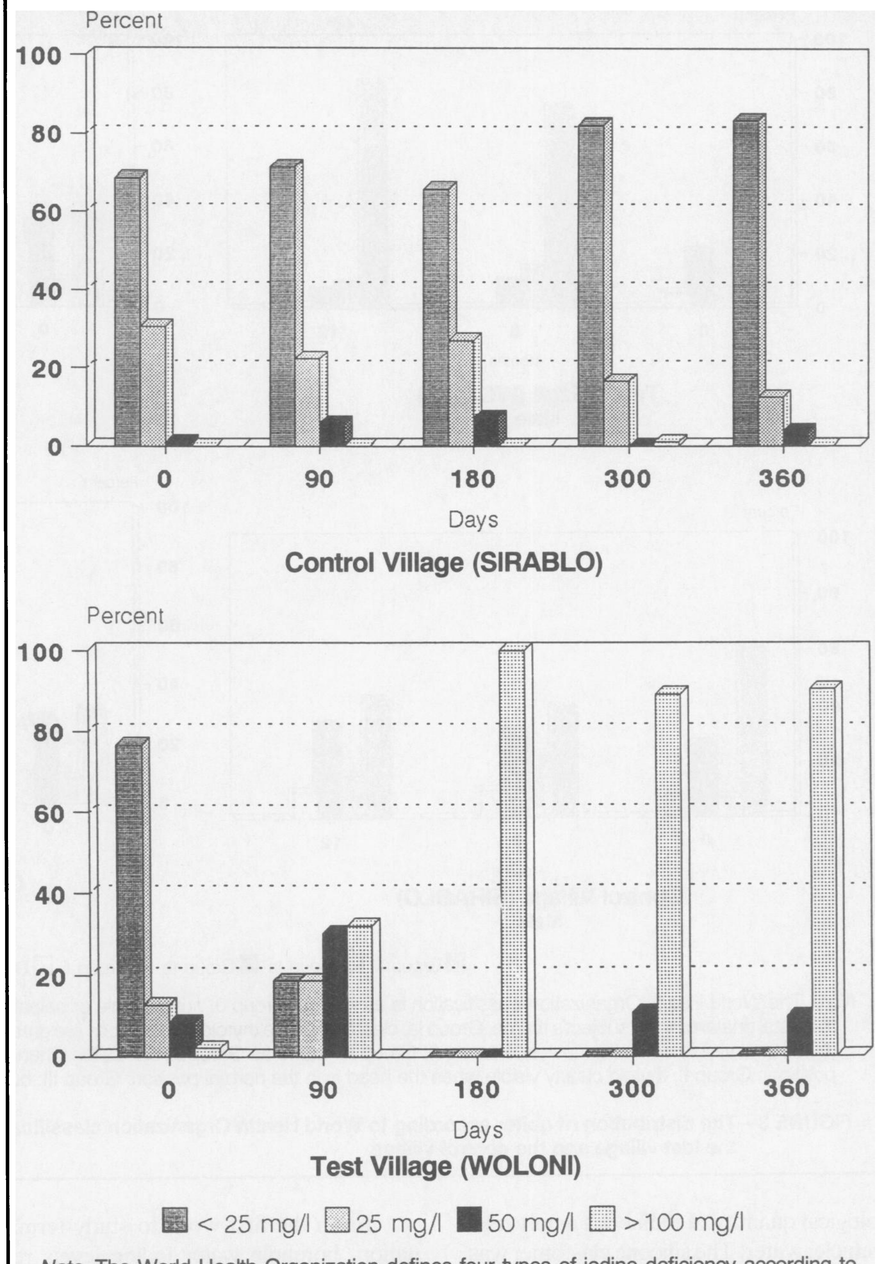
The sample size was 107 subjects for Sirablo and 94 for Woloni. Age and sex distribution in the two populations was close to normal and the two did not differ significantly. The average age was 22 years (SD = 12) at Sirablo and 24 years (SD = 14) at Woloni; there was no statistically significant difference between the sex ratios of the two villages. Ethnic structure (Bambara and Malinke) and eating habits were similar; in both villages, diet is based exclusively on local resources.

Table 1 shows the comparative results for iodine content over the course of time. Before the start of the study, the water supply to the villages had a very low iodine content: the average of eight samples was 4 μg/L and content did not differ significantly between the two villages. Iodine release from the elastomer system in the test village was observed from the 2nd day onward and was continuous throughout the day and constant over the 12-month period; the average concentration for all the assays carried out was 163.2 μg/L (range = 34 to 390 μg/L). The iodine content in the control village water remained unchanged (range = 0 to 7 μg/L).

Table 2 shows the changes in urinary concentrations in the two villages over the course of time. Before the start of the study (day 0), urinary iodine values were low and were not significantly different between the two villages, whether the comparison concerned urinary iodine or the iodine:creatinine ratio. These levels showed that, on average, three quarters of the subjects in the two villages had "severe deficiency," according to the World Health Organization classification.[11]

Figure 2 shows the changes that occurred in urinary iodine levels in the test and control villages according to the degree of deficiency described by the World Health Organization classification. Thus, from 6 months after the installation of the elastomer system until the end of the study, 90.29% of the subjects had "no deficiency" and 9.71% had "slight deficiency"; "moderate" and "severe" deficiencies disappeared at 6 months. There was no significant modification in the control village over the same period.

At the beginning of the study, overall goiter frequency was comparable in the test (53.2%) and control villages (56.5%) ($P = .351$, not significant [NS]). Goiter frequency in males was 40.1% and 39.4% ($P = .894$, NS) in the test and control villages, respectively, and that in females was 66.7% and 68.5% ($P = .666$, NS), respectively. The higher frequency of goiter in females is usual. Twelve months later, the overall frequency of goiters in the test village significantly decreased to 29.2% ($P < .001$). Frequency decreased in both males (16.1%, $P < .001$) and females (44.7%, $P = .04$). Severe forms (GIb and GII) were particularly affected; their frequency relative to all goiter forms fell from 78.4% to 57.3% ($P < .001$). This favorable development was observed as of month 6.



Note. The World Health Organization defines four types of iodine deficiency according to iodine urinary concentrations: iodine < 25 mg/L = severe deficiency; 25 mg/L ≤ iodine < 50 mg/L = moderate deficiency; 50 mg/L ≤ iodine < 100 mg/L = slight deficiency; iodine ≥ 100 mg/L = no deficiency.

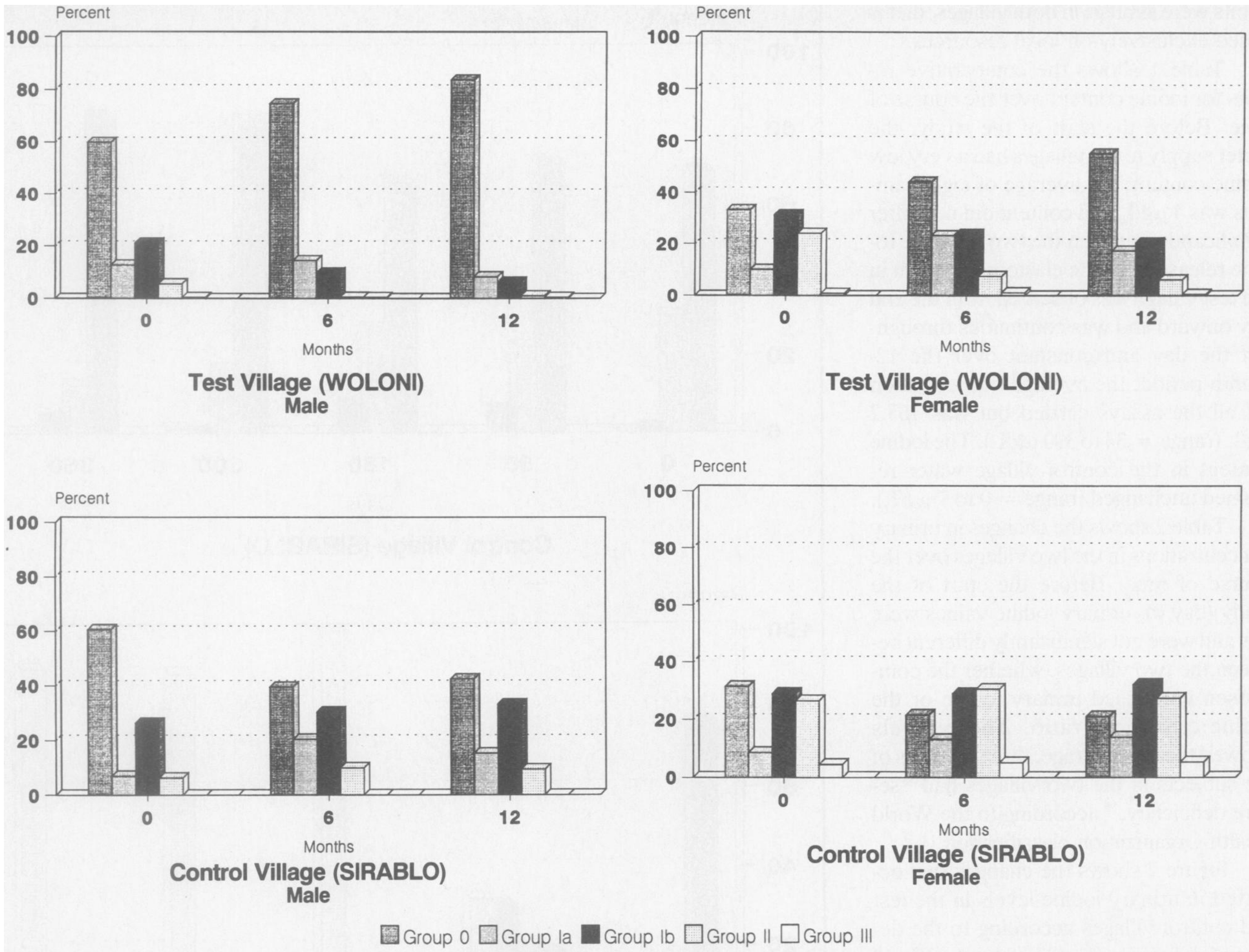
FIGURE 2—Urinary iodine concentrations (μg/L) in subjects in each village at baseline and at 90, 180, 300, and 360 days.

For fibrous GIII goiters, frequency was unchanged. In the control village, no change in goiter frequency was observed. Figures 3A and 3B show the course over time of the various goiter stages, by sex, in the test and control villages.

The elastomer system was easily installed in the boreholes during annual maintenance of the pumping system as recommended by the manufacturers. The device was completely accepted by all the villagers throughout the study. No fears or criticisms were expressed about the device or about the odor or palatability of the water. No clinically detectable adverse effect was noted. No drug containing iodine was introduced into the villages during the entire length of the study.

Discussion

An elastomer system for the controlled release of iodine was designed to provide deficient populations with a phys-



Note. The World Health Organization classification is as follows: Group 0: nonpalpable or palpable thyroid whose lobes are smaller in volume than the distal phalanx of the subject's thumb; Group Ia: clearly palpable thyroid whose lobes are greater in volume than the distal phalanx of the subject's thumb (not visible when the neck is extended); Group Ib: same as Group Ia but visible when the neck is extended (but not visible in the normal position); Group II: thyroid clearly visible when the head is in the normal position; Group III: bulky thyroid, visible from more than 5 m away.

FIGURE 3—The distribution of goiter according to World Health Organization classification at baseline, 6 months, and 12 months for the test village and the control village.

iological quantity of iodine via a universal vehicle: water. The silicone elastomer was an appropriate choice given its properties with regard to the programmed diffusion of molecules such as those of NaI, the absence of toxicity of this type of material, and its stability even under severe storage and transport conditions. The system is particularly suitable for use under realistic conditions in a tropical environment (adaptation to well flow rate, stable diffusion over more than 1 year, know-how for controlled release system installation in boreholes). In the field, the presentation of the device to the study village populations elicited considerable interest. In these highly deficient populations, goiter is considered an everyday public health problem. Installation of the system posed no major technical problems and was effected with the villagers' assistance.

From the first week to study termination, borehole water iodine levels remained stable over time irrespective of season. In the test well, the levels were slightly higher than predicted because the flow rate had been overestimated at <600 L/h. Nonetheless, iodine intake remained within physiological limits. It must be emphasized that toxic levels of iodine require very high intakes (200 to 500 mg per kilogram of body weight per day); long-term intakes of less than 1 to 2 mg per day are considered nonhazardous in humans.[12]

From a methodological viewpoint, it may seem that subject selection would ideally have consisted in recruitment of a cohort of predefined subjects. However, in Africa, an individual's presence in the village depends on subsistence imperatives (agriculture, hunting) that are linked, in particular, to season. It was therefore considered more realistic to randomly select, for each time point, the number of test subjects required. Although this method would increase the intrinsic variance of the results it would prevent the risk of an excessively high number of subjects being lost to follow-up.

The urinary iodine results reflect the excellent compliance of the population. The possibility that the population might reject the intrusion of the system into their nutritional environment was easily overcome by the investigators' educative and informative roles. The persistence of effective iodine intake even after a year of use under realistic tropical conditions was demonstrated by the urinary iodine levels determined, for the test village, in successive assays.

The relative stability of GIa goiter frequency may be explained by the gradual shift of more severe forms toward the left, as shown in Figure 3. The decrease in goiter frequency was significant at 1 year. As of month 6, once thyroid iodine stores had been replenished, urinary iodine levels showed that iodine deficiency had been eradicated from the village. The decrease in goiters appeared regular over time.

The device appears to be appropriate for most iodine-deficient zones in view of its clinical efficacy and the stability and duration of iodine release. It may be positioned in any water source, whether still or flowing. In the case of boreholes, its installation can coincide with the annual maintenance recommended by almost all manufacturers.

For a year, the controlled release system supplies a physiological supplement of iodine that is beneficial for all subjects, whatever their age, sex, nutritional status, or previous medical status, while having no ecological effects. In addition, its large-scale feasibility is not impeded by any of the obstacles that applied to previous methods for combating iodine deficiency. The system provides collective prophylaxis and requires no medical intervention, mobilization, or immobilization of populations. □

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References

1. *Global Strategies for the Prevention and Control of Iodine Deficiency Disorders: Proposals for a Ten-Year Program of Support to Countries.* New York, NY: United Nations, Administrative Committee on Coordination, Subcommittee on Nutrition; 1987. SCN87/IOD A.
2. Hetzel BS, Dunn JT, Stanbury JB, eds. *The Prevention and Control of Iodine Deficiency Disorders.* Amsterdam, The Netherlands: Elsevier; 1987.
3. *Towards the Eradication of Endemic Goiter, Cretinism, and Iodine Deficiency.* Washington, DC: Pan American Health Organization. 1986:28–45. Scientific Publication No. 502.
4. Eltom M, Karisson FA, Bostrom H, Dahlberg PA. The effectiveness of oral iodized oil in treatment and prophylaxis of endemic goiter. *J Clin Endocrinol Metab* 1985;61:1112–1117.
5. Phillips DIW, Lusty TD, Osmond C, Church D. Iodine supplementation: comparison of oral or intramuscular iodized oil with oral potassium iodide. A controlled trial in Zaire. *Int J Epidemiol.* 1988;17:142–147.
6. Warrick EL, Pierce OR, Polmanteer KE, Saam JC. Silicone elastomer development. *Rubber Chem Tech.* 1979;52(3):437–525.
7. *United States Pharmacopeia.* Rockville, Md: US Pharmacopeial Convention. 1985;21:1236.
8. Barrer RM. *Diffusion In and Through Solids.* London, England: Cambridge University Press; 1951.
9. Crank J. *The Mathematics of Diffusion.* New York, NY: Oxford University Press; 1956.
10. Direction Nationale de la Planification. Guide d'identification des problèmes de population et des variables démographiques à intégrer dans les programmes de développement de la République du Mali. Bamako, Mali: Ministère du Plan, République du Mali; 1984.
11. Demayer EM, Lowenstein SW, Thilly CH. *The Control of Endemic Goiter.* Geneva, Switzerland: World Health Organization; 1979.
12. Joint FAO/WHO Expert Committee on Food Additives. *Toxicological Evaluation of Certain Food Additives and Contaminants.* Cambridge, England: Cambridge University Press; 1989:267–294.